

Applicant : Ilya Trakht et al.
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C1 -- HUMAN MONOCLONAL ANTIBODIES AGAINST TUMOR-ASSOCIATED
ANTIGENS --

On page 1, please delete the following paragraph at lines 6-9:

The invention disclosed herein was made with Government support under NIH Grant No. _____ from the Department of Health and Human Services. Accordingly, the U.S. Government has certain rights in this invention.

On page 11, please amend the paragraph at lines 19-21 as follows:

C2 The present invention provides the monoclonal antibody 27.B1 produced by the hybridoma having ATCC Designation No. PTA-1599.

On page 12, please amend the paragraph at lines 1-3 as follows:

C3 The present invention provides the monoclonal antibody 27.F7 produced by the hybridoma having ATCC Designation No. PTA-1598.

On pages 13-19, please amend the paragraphs between page 13, line 23 and page 19, line 14 as follows:

C4 The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with a antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody or Fab fragment thereof being detectably labeled,

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under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; b) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

CY
ul

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with an antibody directed to an epitope on TIP-2 antigen which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any antibody or Fab fragment thereof not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); (c) contacting the antibody 27.F7/Fab fragment-TIP-2 antigen complex of step (b) with a second antibody which specifically binds to the antibody 27.F7/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.F7/Fab fragment-TIP-2 antigen complex; (d) removing any second labeled antibody not bound to the antibody 27.F7/Fab fragment-TIP-2 antigen complex product

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in (c); and (e) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

C4
The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with a antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599 or Fab fragment thereof, said antibody or Fab fragment thereof being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any labeled antibody not bound in the antibody 27.B1-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, or Fab

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C4
fragment thereof under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any antibody/Fab fragment thereof not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (a); (c) contacting the antibody 27.B1/Fab fragment-TIP-2 antigen complex of step (b) with a second antibody which specifically binds to the antibody 27.B1/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.B1/Fab fragment-TIP-2 antigen complex; (d) removing any second labeled antibody not bound to the antibody 27.B1/Fab fragment-TIP-2 antigen complex product in (c); and (e) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598 or an Fab fragment thereof, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2

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antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (b); and (d) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

C4
wf

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (b); (d) contacting the antibody 27.F7/Fab fragment-TIP-2 antigen complex of step (c) with a second antibody which specifically binds to the antibody 27.F7/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.F7/Fab fragment-TIP-2 antigen complex; (e) removing any second labeled antibody not bound to the antibody 27.F7/Fab fragment-TIP-2 antigen complex product in (d); and (f)

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determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody, by detecting the label of second antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

C4
✓
The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any labeled antibody/Fab fragment not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (b); and (d) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal

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antibody 27.B1/Fab fragment produced by the hybridoma designated PTA-1599 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any antibody/Fab fragment not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (b); (d) contacting the antibody 27.B1/Fab fragment-TIP-2 antigen complex of step (c) with a second antibody which specifically binds to the antibody 27.B1/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.B1/Fab fragment-TIP-2 antigen complex; (e) removing any second labeled antibody not bound to the antibody 27.B1/Fab fragment-TIP-2 antigen complex product in (d); and (f) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

The present invention provides an in vivo method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) administering to the subject an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; and (b) determining presence of the

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detectably labeled antibody 27.F7 bound to the surface of cells in the subject, presence of detectably labeled antibody 27.F7 bound to cells indicating diagnosis of cancer in the subject.

Cy
The present invention provides an in vivo method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) administering to the subject an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; and (b) determining presence of the detectably labeled antibody/Fab fragment 27.B1 bound to the surface of cells in the subject, presence of detectably labeled antibody 27.F7/Fab fragment bound to cells indicating diagnosis of cancer in the subject.

On pages 20-21, please amend the paragraph between page 20, line 33 and page 21, line 15 as follows:

C5
The present invention provides a method for immunohistochemical screening of a tissue section from a tumor sample for the presence of TIP-2 antigen bearing cancer cells which comprises: (a) contacting the tissue section from the tumor sample with a detectably labeled antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody/Fab fragment being detectably labeled,

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CS
under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the tissue section; (a) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (b) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On pages 21-25, please amend the paragraphs between page 21, line 27 and page 25, line 35 as follows:

CB
The present invention provides a method for detecting the presence of TIP-2 antigen in biological fluid comprising: (a) contacting a sample of the biological fluid with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any labeled antibody not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen

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complex indicating TIP-2 antigen-bearing human cancer cells in the biological fluid.

CF ✓
The present invention provides a method for detecting the presence of TIP-2 antigen in biological fluid comprising: (a) contacting a sample of the biological fluid with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any labeled antibody not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the biological fluid.

The present invention provides a method for immunohistochemical screening of tissue sections from a tumor sample for the presence of TIP-2 antigen-bearing cancer cells which comprises: (a) contacting the tissue section from the tumor sample with a detectably labeled antibody/Fab fragment directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, said antibody being detectably labeled, under appropriate conditions to bind


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the antibody to TIP-2 antigen on the surface of any cells in the sample; (b) removing any labeled antibody not bound to the cells in the sample; and (c) determining presence of antibody 27.B1 bound to the cells in the sample, presence of antibody 27.B1 bound to cells indicating TIP-2 antigen-bearing cancer cells in the tumor sample.

CP
The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining presence of detectably labeled antibody 27.F7/Fab fragment bound to the surface of cells in the subject according to the above-described method of detecting TIP-2 antigen on the surface of cancer cells in a sample; (c) comparing the presence of detectably labeled antibody/Fab fragment 27.F7 bound to cells in step (b) with the presence of detectably labeled antibody 27.F7 bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater presence of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser presence of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or

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(ii) after treatment indicates regression of the cancer in the subject.

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining presence of detectably labeled antibody 27.B1/Fab fragment bound to the surface of cells in the subject according to the above-described method for detecting TIP-2 antigen on the surface of cancer cells in a sample; (c) comparing the presence of detectably labeled antibody/Fab fragment 27.B1 bound to cells in step (b) with the presence of detectably labeled antibody 27.B1/Fab fragment bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater presence of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser presence of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2

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CF
antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining quantity of detectably labeled antibody 27.F7/Fab fragment bound to the surface of cells in the subject according to the above-described method for detecting TIP-2 antigen on the surface of cancer cells in a sample; (c) comparing the quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) with the presence of detectably labeled antibody 27.F7/Fab fragment bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with the cancer an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-

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1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining quantity of detectably labeled antibody 27.B1/Fab fragment bound to the surface of cells in the subject according to the above-described method; and (c) comparing the quantity of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) with the presence of detectably labeled antibody 27.B1 bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater quantity of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser quantity of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

On page 39, please amend the paragraph between lines 14-23 as follows:

This invention also provides human hybridoma fusion partner cell line heteromyeloma B6B11, and human hybridoma fusion partner cell line trioma MFP-2. These hybridoma cell lines were deposited on March 17, 1998 with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, U.S.A., under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. These hybridomas have been accorded ATCC Designation Nos. HB-12481 and HB-12482 respectively.

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On pages 56-57, please amend the paragraphs between page 56, line 13 and page 57, line 4 as follows:

08
The present invention provides a monoclonal antibody which specifically binds and forms a complex with TIP-2 antigen located on the surface of human cancer cells, the TIP-2 antigen being an antigen to which monoclonal antibody 27.B1 specifically binds. According to certain embodiments of the present invention, the monoclonal antibody of the invention is a murine monoclonal antibody, a chimaeric monoclonal antibody, a humanized monoclonal antibody, or a human monoclonal antibody. In an embodiment of the present invention, the monoclonal antibody of the invention is capable of binding to the epitope which is specifically recognized by monoclonal antibody 27.B1 produced by the hybridoma having ATCC Designation No. PTA-1599.

The present invention provides the monoclonal antibody 27.B1 produced by the hybridoma having ATCC Designation No. PTA-1599.

The present invention provides a hybridoma cell producing the monoclonal antibody of this invention. In an embodiment of the invention, the hybridoma cell has ATCC Designation No. PTA-1599.

Hybridoma 27.B1 was deposited on March 28, 2000 with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent

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C8
Procedure. 27.B1 was accorded ATCC Designation No. PTA-1599.

On pages 57-58, please amend the paragraphs between page 57, line 27 and page 58, line 19 as follows:

C9
The present invention provides a monoclonal antibody which specifically binds and forms a complex with TIP-2 antigen located on the surface of human cancer cells, the TIP-2 antigen being an antigen to which monoclonal antibody 27.F7 specifically binds. According to certain embodiments of the present invention, the monoclonal antibody of the invention is a murine monoclonal antibody, a chimaeric monoclonal antibody, a humanized monoclonal antibody, or a human monoclonal antibody. In an embodiment of the present invention, the monoclonal antibody of the invention is capable of binding to the epitope which is specifically recognized by monoclonal antibody 27.F7 produced by the hybridoma having ATCC Designation No. PTA-1598.

The present invention provides the monoclonal antibody 27.F7 produced by the hybridoma having ATCC Designation No. PTA-1598.

The present invention provides a hybridoma cell producing the monoclonal antibody of this invention. In an embodiment of the invention, the hybridoma cell has ATCC Designation No. PTA-1598.

Hybridoma 27.F7 was deposited on March 28, 2000 with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent

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C9

Procedure. 27.F7 was accorded ATCC Designation No. PTA-1598.

On pages 62-63, please amend the paragraph between page 62, line 23 and page 63, line 2 as follows:

C10

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with a antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody or Fab fragment thereof being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On page 64, please amend the paragraph between lines 1-27 as follows:

C11

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with an antibody directed to an epitope on TIP-2 antigen which epitope is

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CLL
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recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any antibody or Fab fragment thereof not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); (c) contacting the antibody 27.F7/Fab fragment-TIP-2 antigen complex of step (b) with a second antibody which specifically binds to the antibody 27.F7/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.F7/Fab fragment-TIP-2 antigen complex; (d) removing any second labeled antibody not bound to the antibody 27.F7/Fab fragment-TIP-2 antigen complex product in (c); and (e) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On pages 65-66, please amend the paragraph between page 65, line 25 and page 66, line 4 as follows:

C.12

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA0-1599 or Fab

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C12
UP

fragment thereof, said antibody or Fab fragment thereof being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any labeled antibody not bound in the antibody 27.B1-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On page 67, please amend the paragraph between lines 4-30 as follows:

C13

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, or Fab fragment thereof under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any antibody/Fab fragment thereof not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (a); (c) contacting the antibody 27.B1/Fab fragment-TIP-2 antigen complex of step (b) with a second antibody which specifically binds to the antibody 27.B1/Fab fragment-TIP-2 antigen complex, said second antibody being detectably

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C13
labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.B1/Fab fragment-TIP-2 antigen complex; (d) removing any second labeled antibody not bound to the antibody 27.B1/Fab fragment-TIP-2 antigen complex product in (c); and (e) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On pages 68-69, please amend the paragraph between page 68, line 28 and page 69, line 8 as follows:

C14
The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598 or an Fab fragment thereof, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (b); and (d) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody,

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C44
64 presence of antibody 27.F7/Fab fragment-TIP-2 antigen
complex indicating diagnosis of cancer in the subject.

On page 70, please amend the paragraph between lines 4-30 as follows:

C15
The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (b); (d) contacting the antibody 27.F7/Fab fragment-TIP-2 antigen complex of step (c) with a second antibody which specifically binds to the antibody 27.F7/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.F7/Fab fragment-TIP-2 antigen complex; (e) removing any second labeled antibody not bound to the antibody 27.F7/Fab fragment-TIP-2 antigen complex product in (d); and (f) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.F7/Fab fragment-

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C15
✓ TIP-2 antigen complex indicating diagnosis of cancer in the subject.

On pages 71-72, please amend the paragraph between page 71, line 26 and page 72, line 6 as follows:

C16
The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any labeled antibody/Fab fragment not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (b); and (d) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

On page 73, please amend the paragraph between lines 4-30 as follows:

C17
The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the

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C17
M

subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1/Fab fragment produced by the hybridoma designated PTA-1599 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any antibody/Fab fragment not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (b); (d) contacting the antibody 27.B1/Fab fragment-TIP-2 antigen complex of step (c) with a second antibody which specifically binds to the antibody 27.B1/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.B1/Fab fragment-TIP-2 antigen complex; (e) removing any second labeled antibody not bound to the antibody 27.B1/Fab fragment-TIP-2 antigen complex product in (d); and (f) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

On pages 74-75, please amend the paragraph between page 74, line 26 and page 75, line 2 as follows:

C18

The present invention provides an in vivo method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) administering to the subject an antibody directed to an epitope on TIP-2

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CLX
antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; and (b) determining presence of the detectably labeled antibody 27.F7 bound to the surface of cells in the subject, presence of detectably labeled antibody 27.F7 bound to cells indicating diagnosis of cancer in the subject.

On pages 75-76, please amend the paragraph between page 75, line 35 and page 76, line 10 as follows:

CL9
The present invention provides an in vivo method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) administering to the subject an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; and (b) determining presence of the detectably labeled antibody/Fab fragment 27.B1 bound to the surface of cells in the subject, presence of detectably labeled antibody 27.F7/Fab fragment bound to cells indicating diagnosis of cancer in the subject.

On page 81, please amend the paragraph between lines 12-31 as follows:

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C20
The present invention provides a method for immunohistochemical screening of a tissue section from a tumor sample for the presence of TIP-2 antigen bearing cancer cells which comprises: (a) contacting the tissue section from the tumor sample with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody/Fab fragment being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the tissue section; (a) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (b) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On pages 82-83, please amend the paragraphs between page 72, line 35 and page 83, line 14 as follows:

C21
In an embodiment of this invention the monoclonal antibody directed to the epitope on TIP-2 antigen is human monoclonal antibody 27.F7 directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598.

In an embodiment of this invention the monoclonal antibody directed to the epitope on TIP-2 antigen is human

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monoclonal antibody 27.B1 directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599.

C²¹
C⁴

In an embodiment of this invention the monoclonal antibody directed to the epitope of TIP-2 antigen is murine monoclonal antibody directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal antibody produced by the hybridoma designated PTA-1599.

On page 84, please amend the paragraph between lines 10-27 as follows:

The present invention provides a method for detecting the presence of TIP-2 antigen in biological fluid comprising:
(a) contacting a sample of the biological fluid with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any labeled antibody not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (d) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the biological fluid.

C²²

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On page 85, please amend the paragraphs between lines 19-29 as follows:

C23
In an embodiment of this invention the monoclonal antibody directed to the epitope on TIP-2 antigen is human monoclonal antibody 27.F7 directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598.

In an embodiment of this invention the monoclonal antibody directed to the epitope on TIP-2 antigen is human monoclonal antibody 27.B1 directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599.

On page 86, please amend the paragraph between lines 1-17 as follows:

C24
The present invention provides a method for immunohistochemical screening of tissue sections from a tumor sample for the presence of TIP-2 antigen-bearing cancer cells which comprises: (a) contacting the tissue section from the tumor sample with a detectably labeled antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the sample; (b) removing any labeled antibody not bound to the cells in the sample; and (c) determining presence of antibody 27.B1 bound to the cells in the sample, presence of antibody

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C24 27.B1 bound to cells indicating TIP-2 antigen-bearing cancer cells in the tumor sample.

On page 87, please amend the paragraph between lines 8-32 as follows:

C25 The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining presence of detectably labeled antibody 27.F7/Fab fragment bound to the surface of cells in the subject according to the instant method; and (c) comparing the presence of detectably labeled antibody/Fab fragment 27.F7 bound to cells in step (b) with the presence of detectably labeled antibody 27.F7 bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater presence of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser presence of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

On pages 88-89, please amend the paragraphs between page 88, line

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25 and page 89, line 11 as follows:

C26
The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining presence of detectably labeled antibody 27.B1/Fab fragment bound to the surface of cells in the subject according to the instant method; and (c) comparing the presence of detectably labeled antibody/Fab fragment 27.B1 bound to cells in step (b) with the presence of detectably labeled antibody 27.B1/Fab fragment bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater presence of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser presence of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

On page 90, please amend the paragraph between lines 4-28 as follows:

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C 27

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated PTA-1598, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining quantity of detectably labeled antibody 27.F7/Fab fragment bound to the surface of cells in the subject according to the instant method; and (c) comparing the quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) with the presence of detectably labeled antibody 27.F7/Fab fragment bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

On page 92, please amend the paragraph between lines 11-35 as follows:

C 28

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a)